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Graphical Abstract





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Conversion of α,β -unsaturated ketones to 1,5-diones *via* tandem retro-Aldol and Michael addition using Co(acac)₂ covalently anchored onto amine functionalized silica

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ABSTRACT

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Keywords: AS-Co(acac)₂ a,β -unsaturated ketones 1,5-diones Retro-Aldol Michael addition Heterogeneous catalysis A new and efficient method has been developed for the conversion of α,β -unsaturated ketones to 1,5diketones *via* tandem retro-Aldol and Michael addition in the presence of Co(acac)₂ covalently anchored amine functionalized silica [AS-Co(acac)₂]. The single crystal X-ray crystallography confirms the formation of 1,5-diketones. This method has been proved to be an attractive alternative to existing methodologies under conventional homogeneous catalysis with the frequent troublesome manipulation and work-up. The AS-Co(acac)₂ was found to be highly active and could be recycled for four consecutive runs with slight decrease in activity.

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Introduction

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially, interest has been focused on the synthesis and biodynamic activities of chalcones. Due to the unique structural feature, chalcones have also emerged as a reliable class of substrates and important precursors in synthetic chemistry. Their activity is mostly based either on the Michael acceptor activity of the a,β -unsaturated carbonyl system, or their radical scavenging or reductive potential which are often referred to as their antioxidative behaviour.¹ Moreover, they have attracted widespread research interests from organic chemists to investigate their chemical reactivities in a variety of reactions, e.g. classical Claisen-Schmidt condensation,² Suzuki coupling³ and Heck reaction.⁴

Epoxy carbonyl compounds are very important intermediates and can serve as versatile precursors in the synthesis of many natural products and drug molecules. These are usually prepared *via* epoxidation of α,β -unsaturated ketones. In an initial attempt to evaluate the catalytic activity of AS-Co(acac)₂ for the epoxidation, we examined the reaction in detail using (*E*)-1,3bis(4-chlorophenyl)prop-2-en-1-one as a test substrate in the presence of aq. NaOH using 1,4-dioxane as solvent (**Scheme 1**). During the course of characterization, to our surprise it was found that the product was quite different from the desired product. From the ¹H NMR spectral data, it was found that there was no peak corresponding to -CH proton of oxirane ring, whereas additional peaks appeared as double-doublets in the range δ 3.2-



Scheme 1. Conversion of α , β -unsaturated ketones to 1,5-diones *via* tandem retro-Aldol and Michael addition.

3.4 and multiplet in the range δ 4.0-4.2 suggesting the presence of -CH2-CH moiety in the isolated product.Various possibilities were explored and it was found that in case of α,β -unsaturated ketones, carbonyl group in conjugation with the olefin double bond can activate the olefin double bond and cause it to break into aldehyde and ketone in the presence of alkali, heat and water (retro-Aldol). Although the retro-aldol reaction is less widespread, it nevertheless plays an important role in solving certain synthetic tasks.⁵ The lack of a general and effective method for the retro-Aldol reaction is often a restriction for its more widespread use in organic synthesis. The ketone generated by retro-Aldol in the presence of alkali and AS-Co(acac)₂ undergoes Michael addition on α,β -unsaturated ketone to give 1,5-diketone, structure of which was confirmed by ¹H, ¹³C NMR, and mass spectral data. Single crystal X-ray crystallography further confirmed the formation of 1,3,5-tris(4chlorophenyl)pentane-1,5-dione. The Michael addition reaction is one of the most fundamental reactions in the synthesis of 1,5 dicarbonyl compounds. Transition-metal-catalyzed Michael

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addition of organometallic species over the last two decades has become an important synthetic tool for constructing carbon skeletons.⁶⁷ The Michael addition of active methylene compounds to activated π -systems is one of the oldest and more useful carbon-carbon bond forming reactions.⁸⁻⁹ Michael addition of malonate diesters¹⁰ or nitroalkanes¹¹ to simple enones have been reported. Alternatively, in pioneering work by Barbas et al. and other groups, simple ketones or aldehydes have been added to activated Michael acceptors such as nitroalkenes or alkylidenemalonates.¹² In contrast, Michael addition reaction of ketones with chalcones still remain a challenge and are rarely reported, probably due to the low reactivity and high steric hindrance of substrate. Diketones are one of the important synthetic intermediates and desirable starting materials for the synthesis of numerous heterocycles¹³⁻¹⁵ and polyfunctional compounds.¹⁶⁻¹⁹ Polyfunctionalized derivatives containing a dicarbonyl moiety are valuable intermediates in organic synthesis since they can be transformed into a plethora of important target compounds such as cyclopentenones, furans, pyrroles, thiophenes and other heterocyclic systems.²⁰⁻²⁷

Since we found an unexpected reaction taking place, we set out to study the scope of the reaction. Toward this goal, we have varied reaction conditions such as the catalyst, base and the solvent. Initial investigations for the conversion of α , β unsaturated carbonyl compounds to diketones involved the use of different supported metal catalysts using (*E*)-1,3-bis(4chlorophenyl)prop-2-en-1-one as a test substrate. Out of the different catalysts tested, AS-Co(acac)₂ gave the best results with maximum yield. The results are summarized in **Table 1**.

Table 1. Comparison of the catalytic activities of different $M(acac)_n$ covalently anchored onto amine functionalized silica for the synthesis of 1,5-diones

| Entry | Catalyst | Time (h) | Yield (%) ^b |
|-------|--------------------------|----------|------------------------|
| 1 | AS-Co(acac) ₂ | 5 | 48 |
| 2 | AS-Cu(acac) ₂ | 5 | 30 |
| 3 | AS-Pd(acac) ₂ | 5 | 35 |
| 4 | AS-Mn(acac) ₃ | 5 | 40 |
| 5 | AS-Co(acac) ₃ | 5 | 40 |
| 6 | AS-Ru(acac) ₃ | 5 | 20 |

^aReaction conditions: (E)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (0.277 g, 1 mmol), 25 equiv. NaOH (2 mL, 0.25 M solution), AS-M(acac)_n [M= Cu, Ru, Pd, Co, Mn and n=2 or 3 (5 mol% metal)] at 80 °C in 1,4-dioxane (10 mL).

^bColumn chromatography yields.

The preparation and characterization of $AS-Co(acac)_2$ has already been reported in our earlier communication.²⁸

The effect of different solvents at different temperatures on the catalytic activity of AS-Co(acac)₂ was investigated. We varied the solvent used in the reaction to evaluate its role and efficacy. Among the different solvents tested (toluene, water, *tert*-butanol, 1,4-dioxane), the reaction proceeded well in 1,4-dioxane at 80 °C in terms of activity and selectivity (**Table 2**). The reaction was very sluggish in the absence of base. Next, we tested different bases (K₂CO₃, KOH, NaOH) and found that NaOH gave the best results with maximum conversion. From the above observation, it appeared that the presence of base is detrimental for the formation of retro-Aldol product. Having developed conditions for this unique reaction, the work was focused on the

investigation of structure-reactivity relationship. Thus, a variety of chalcones were synthesized and subjected to reaction under the optimized conditions.²⁹ The reaction led to the desired products in moderate yields. The moderate yield of isolated products is due to the fact that some amount of the chalcone undergoes retro-Aldol to yield ketone and aldehyde, while the other remained as it is. The left out chalcone act as Michael acceptor and the enolate ion generated from ketone act as nucleophile. The reported yield of products is with respect to remaining chalcone, so products were obtained in low yields.

Table 2. Effect of solvent and temperature on the conversion of α,β -unsaturated carbonyl compounds to 1,5-diketones

| Columnt | T | Timer (b) | Viold (07) ^b |
|-------------|-------------|-----------|-------------------------|
| Solvent | Temperature | Time (n) | rield (%) |
| Toluene | 110 °C | 7 | No reaction |
| Water | 50 °C | 7 | Traces |
| Water | 100 °C | 7 | 10 |
| ter-Butanol | 50 °C | 7 | 15 |
| ter-Butanol | 82 °C | 7 | 30 |
| 1,4-Dioxane | 50 °C | 7 | 30 |
| 1,4-Dioxane | 80 °C | 5 | 48 |
| 1,4-Dioxane | 80 °C | 7 | 48 |

^aReaction conditions: (*E*)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (0.277 g, 1 mmol), 25 equiv. NaOH (2 mL, 0.25 M solution), AS-Co(acac)_n (0.2 g, 1.45 wt% Co) at 80 $^{\circ}$ C in 1,4-dioxane (10 mL). ^bColumn chromatography yields.

The substituent has significant effect on the reaction efficiency and reactivity. R_1 and R_2 bearing chloro, bromo or nitro group on aromatic ring (Scheme 1) led to the product in good yields (Table 3, entries 1-3, 5-6), whereas, reactant bearing electrondonating group took longer time and gave the desired product in moderate yield (Table 3, entry 4). The structure of 1,3,5-tris(4chlorophenyl)pentane-1,5-dione has been confirmed by X-ray crystallography (Table 3, entry 1, S1).



Fig 1. *ORTEP* view of 1,3,5-tris(4-chlorophenyl)pentane-1,5-dione.

Heterocyclic chalcones were also found to be compatible under the optimized reaction conditions and converted to the corresponding products in good yields (entries 7,8). Overall, there is a good substrate scope for the reaction, providing access to a variety of 1,5-diketones in high selectivities. The separation

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of 1,5-diketones from the accompanying aromatic aldehydes has been effectively achieved by column chromatography (Table 3, S8, S9). Although great efforts have been devoted to the synthetic and selectivity aspects of Michael reactions catalyzed by transition metals, less effort has been dedicated to the mechanistic aspects, which is crucial for their better understanding. The mechanistic pathway of the reaction can be explained by the retro-Aldol and Michael addition of ketone on α,β -unsaturated ketones. The proposed mechanism involves the retro-Aldol reaction of the α,β -unsaturated ketones, thus breaking it into aldehyde and ketone. The C=O bond of the chalcone interacts with the metal catalyst thus weakening the π -bond followed by nucleophilic attack of enolate ion (generated by the reaction of base with ketone) to give the desired 1,5-diketone with the regeneration of the metal catalyst (Fig. 2). Further, crossover experiment was carried out to study and explore the mechanistic pathway of the reaction using (E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one and (E)-3-(4-chloro phenyl)-1-(4methylphenyl)prop-2-en-1-one as test substrates. The aim of the experiment was to determine whether the components of each reactant had an opportunity to exchange with each other i.e. intra or intermolecular mechanistic path. The structural analysis of the isolated product confirms the formation of intermolecular cross product. From the two substrates, 3-(4-chlorophenyl)-1-phenyl-5-(4-methylphenyl)pentane-1,5-dione was formed exclusively along with the mixture of two unreacted chalcones. The formation of the single crossover product can be explained by the fact that out of the two reacting species, (E)-3-(4-nitrophenyl)-1undergoes retro-Aldol faster resulting phenylprop-2-en-1-one in the formation of 4-nitrobenzaldehyde and acetophenone. However, case of (E)-3-(4-chlorophenyl)-1-(4in methylphenyl)prop-2-en-1-one, the presence of electron donating group reduces the chance of retro-Aldol and thus make the reaction process slow. In the meantime, the acetophenone in presence of base generates enolate and undergoes Michael addition with (E)-3-(4-chloro phenyl)-1-(4-methylphenyl)prop-2give 3-(4-chlorophenyl)-1-phenyl-5-(4en-1-one to methylphenyl)pentane-1,5-dione as the product.



Fig 2. Proposed mechanism for the synthesis of 1,5-diketones via retro-Aldol and Michael addition using AS-Co(acac)₂.

In order to find out the role of AS-Co(acac)₂ as the heterogeneous catalyst, the reaction with (E)-1,3-bis(4-chlorophenyl)prop-2-en-1-one was carried out in the presence of activated silica, 3aminopropyl silica (AMPS) and without using catalyst (Table 4, entry 1). With AS-Co(acac)₂, reaction was completed in 5 h with 48% yield (column chromatography). However, with activated silica and AMPS, poor results were obtained with negligible conversion of the reactant. The results are summarized in Table 4, which indicated that the presence of cobalt played an important role for the desired transformation.

Table 3. AS-Co(acac)₂ catalyzed synthesis of 1,5-diketones from α,β -unsaturated carbonyl compounds *via* retro-aldol and Michael addition^a



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^aReaction conditions: α,β -unsaturated carbonyl compound (1 mmol), 0.025 equiv. NaOH (2 mL, 2.5 M solution), AS-Co(acac)₂, (0.2 g, 1.45 wt% Co) at 80 °C in 1,4-dioxane (10 mL).

^bAll the yields refer to column chromatography.

^cCross over experiment: (E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1one (1 mmol), (E)-3-(4-chloro phenyl)-1-(4-methylphenyl)prop-2en-1-one (1 mmol) as test substrates and reaction conditions as mentioned above.

^dMixture: mixture of two chalcones and aldehyde.

Table 4. Comparison of activity of AS-Co(acac)₂, activated silica and AMPS for the conversion of α,β -unsaturated carbonyl compounds to diketones^a.

| st | 5 | 5 |
|-------------------|--|------------------------------|
| silica | 5 | 10 |
| opyl silica | 5 | 10 |
| cac) ₂ | 5 | 48 |
| | silica pyl silica ac) ₂ | silica5pyl silica5 $ac)_2$ 5 |

^aReaction conditions: (E)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (0.277 g, 1 mmol), 0.025 equiv. NaOH (2 mL, 2.5 M solution), and catalyst (0.2 g, 1.45 wt% Co for entry 4; 0.2 g for entries 2-3) at 80 ^oC in 1,4- dioxane (10 mL). ^bColumn chromatography yields.

The recovery and recyclability of AS-Co(acac)₂ catalyst was investigated for the synthesis of 1,5-diketones for four consecutive runs (Fig. 3) and found that there is a little drop in the activity of the catalyst upto 4th run. At the end of the reaction, the catalyst was separated by simple filtration, washed with ethyl acetate (3×5 mL) and water (3×10 mL), followed by drying before using in the next run. The amount of Co in the recovered catalyst was determined by AAS after 4th run. The results showed that the Co content of the recovered catalyst remains almost constant. This fact confirmed the strong coordination of $Co(acac)_2$ with amine functionalized silica.

Conclusion

In conclusion, we have developed a new and efficient approach. for the synthesis of 1,5-diketones from α,β -unsaturated carbonyl compounds via tandem retro-Aldol and Michael addition reactions. We believe this is the first report on the synthesis of 1,5-diketones following this strategy. The method provides an

attractive alternative to conventional homogeneous catalysts with easy work-up and recyclability.



Fig 3. Recyclability of AS-Co(acac)₂. Reaction conditions: (E)-1,3bis(4-chlorophenyl)prop-2-en-1-one (0.277 g, 1 mmol), 0.025 equiv. NaOH (2 mL, 2.5 M solution), AS-Co(acac)₂, (0.2 g, 1.45 wt% Co) at 80 °C in 1,4-dioxane (10 mL) for 5 h.

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- 29. General procedure for the AS-Co(acac)₂ catalyzed conversion of σ , β -unsaturated carbonyl compounds to 1,5-diketones

To a mixture of α,β -unsaturated carbonyl compound (1 mmol), 0.025 equiv. NaOH (2 mL, 2.5 M solution) and AS-Co(acac)₂ (0.2 g, 1.45 wt% Co), 1,4-dioxane (10 mL) was added, and the reaction mixture was stirred at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate and filtered. The residue was washed with hot ethyl acetate (30 mL), followed by distilled water (150 mL). The organic layer was washed with water and dried over anhydrous Na₂SO₄. Finally, the product was obtained after purification by column chromatography on silica gel (EtOAc-pet. ether). The recovered catalyst was washed with EtOAc (3×5 mL) followed by double distilled water (3×10 mL), dried at 100 °C for 2 h and reused for subsequent reactions.

The structures of the products were confirmed by 1 H, 13 C NMR and mass spectral data (S10).

Representative spectral of 1,3,5-tris(4-Chlorophenyl)pentane-1,5-dione (Table 3, entry 1). M.p. 123-125 °C, yield 0.066 g (48%). ¹H NMR (400 MHz, CDCl₃): δ 3.26-3.32 (dd, 2H, J= 8 Hz, J= 16 Hz, CH₂), 3.45-3.51 (dd, 2H, J= 8 Hz, J= 16 Hz, CH₂), 4.01-4.05 (m, 1H, CH), 7.21-7.28 (m, 4H, Harom), 7.44-7.46 (d, 4H, J= 8 Hz, Harom), 7.89-7.91 (d, 4H, J= 8 Hz, Harom). ¹³C NMR (100 MHz, CDCl₃): 36.41, 44.64, 128.84, 128.86, 129.02, 129.54, 132.56, 134.95, 139.79, 141.96, 196.99. MS (ESI): 430 (M)⁺, 432.90 (M+2).

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